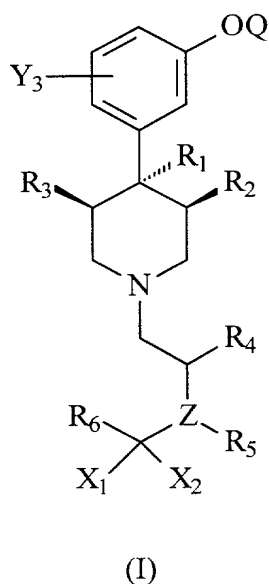


Claims:

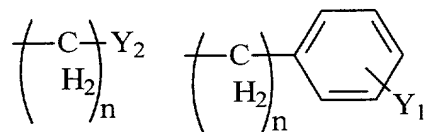
1. A method of binding a kappa opioid receptor in a subject in need thereof, comprising:

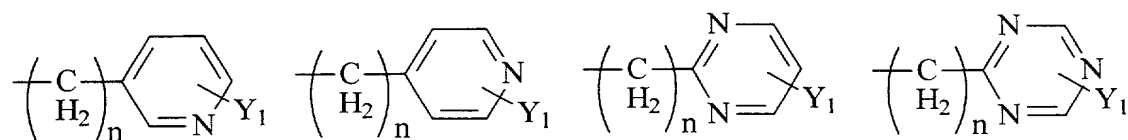
administering to said subject a composition comprising a kappa opioid receptor antagonist and a physiologically acceptable carrier, wherein the kappa opioid receptor antagonist is a compound of formula (I):



wherein Q is H or COC₁₋₈ alkyl;

R₁ is C₁₋₈ alkyl, or one of the following structures:





Y₁ is H, OH, Br, Cl, F, CN, CF₃, NO₂, N₃, OR₈, CO₂R₉, C₁₋₆ alkyl, NR₁₀R₁₁, NHCOR₁₂, NHCO₂R₁₂, CONR₁₃R₁₄, CH₂(CH₂)_nY₂;

Y₂ is H, CF₃, CO₂R₉, C₁₋₆alkyl, NR₁₀R₁₁, NHCOR₁₂, NHCO₂R₁₂, CONR₁₃R₁₄, CH₂OH, CH₂OR₈, COCH₂R₉;

Y₃ is H, OH, Br, Cl, F, CN, CF₃, NO₂, N₃, OR₈, CO₂R₉, C₁₋₆ alkyl, NR₁₀R₁₁, NHCOR₁₂, NHCO₂R₁₂, CONR₁₃R₁₄, CH₂(CH₂)_nY₂;

R₂ is H, C₁₋₈ alkyl, C₃₋₈ alkenyl, C₃₋₈ alkynyl or CH₂aryl substituted by one or more groups Y₁;

R₃ is H, C₁₋₈ alkyl, C₃₋₈ alkenyl, C₃₋₈ alkynyl or CH₂aryl substituted by one or more groups Y₁,

wherein R₂ and R₃ may be bonded together to form a C₂₋₈ alkyl group;

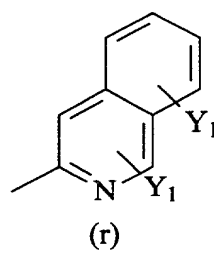
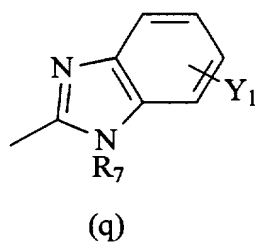
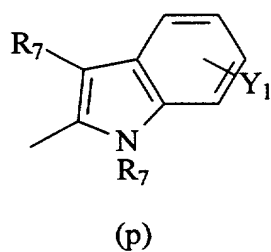
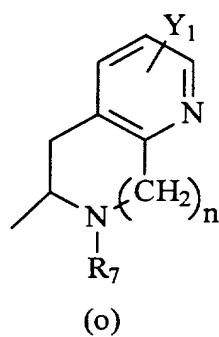
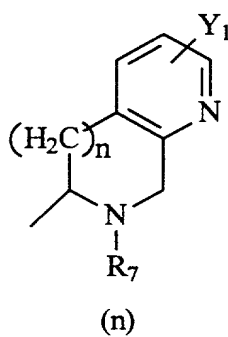
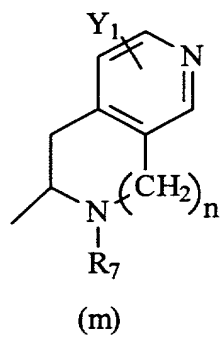
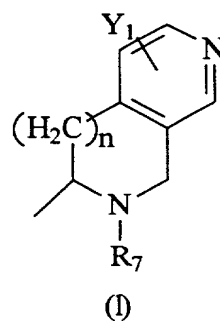
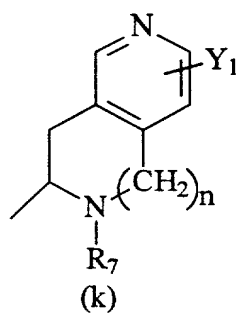
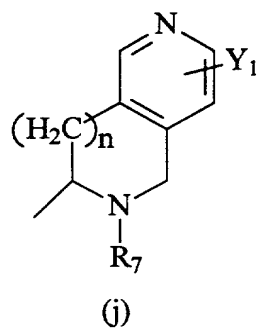
R₄ is hydrogen, C₁₋₈ alkyl, CO₂C₁₋₈ alkylaryl substituted by one or more groups Y₁, CH₂aryl substituted by one or more groups Y₁ or CO₂C₁₋₈ alkyl;

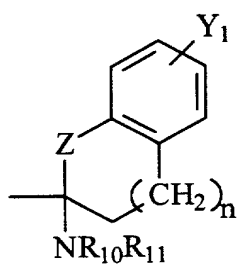
Z is N, O or S; where Z is O or S, there is no R₅

R₅ is H, C₁₋₈ alkyl, C₃₋₈ alkenyl, C₃₋₈ alkynyl, CH₂CO₂C₁₋₈ alkyl, CO₂C₁₋₈ alkyl or CH₂aryl substituted by one or more groups Y₁;

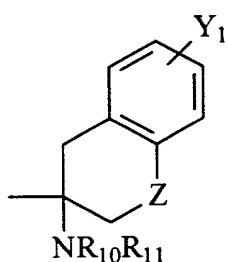
n is 0, 1, 2 or 3;

R₆ is a group selected from the group consisting of structures (a)-(bbb):

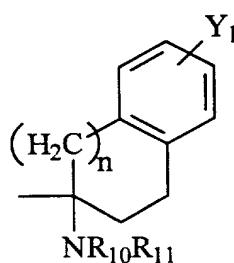




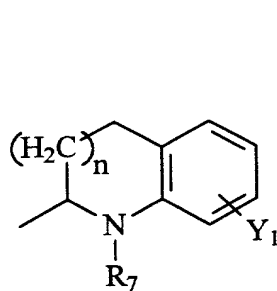
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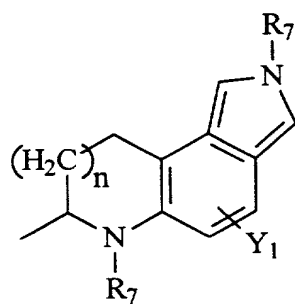
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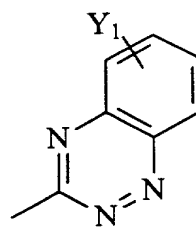
(u)



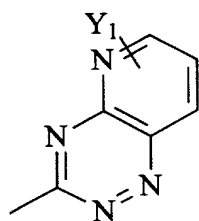
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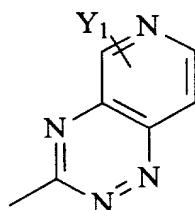
(w)



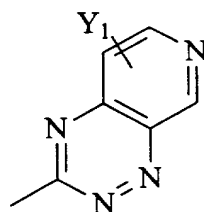
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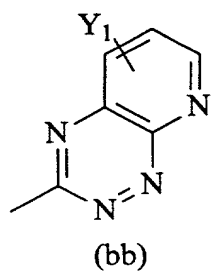
(y)



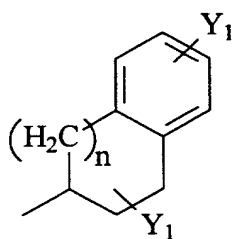
(z)



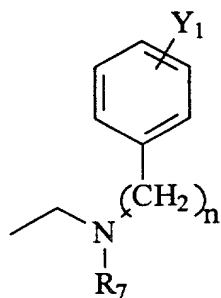
(aa)



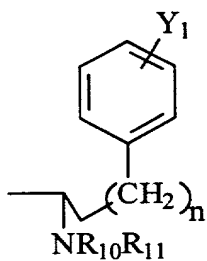
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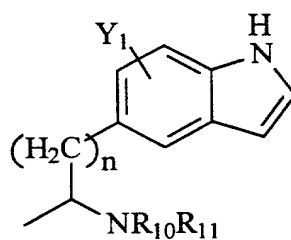
(cc)



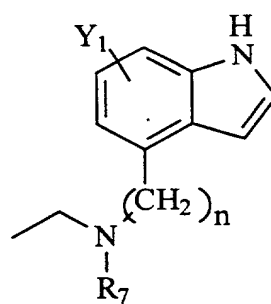
(dd)



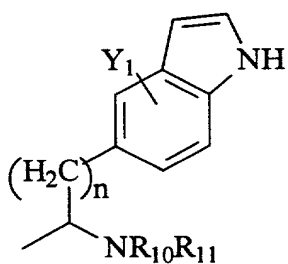
(ee)



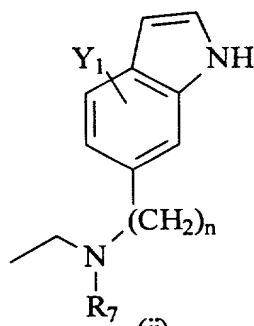
(ff)



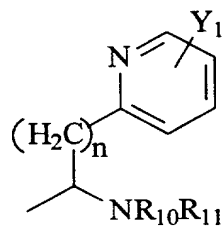
(gg)



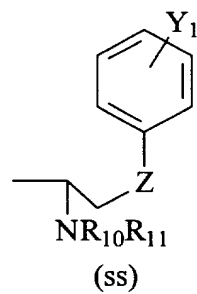
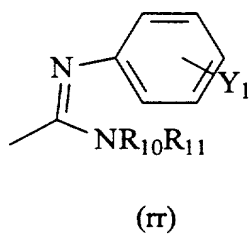
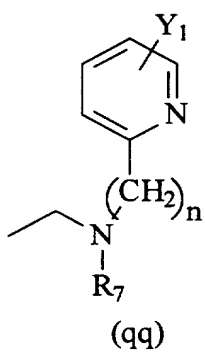
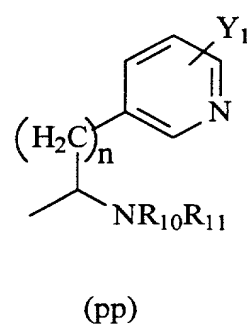
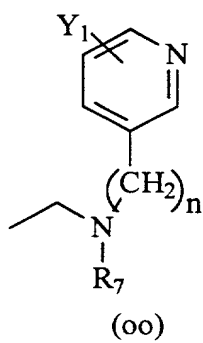
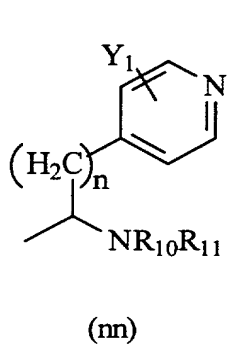
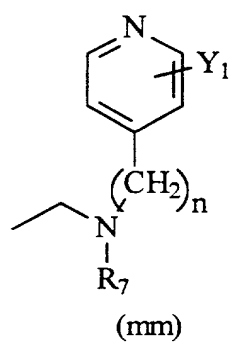
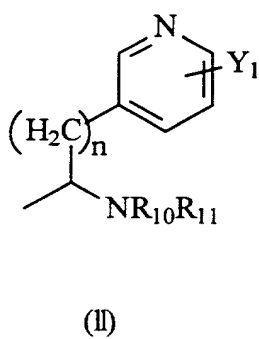
(hh)

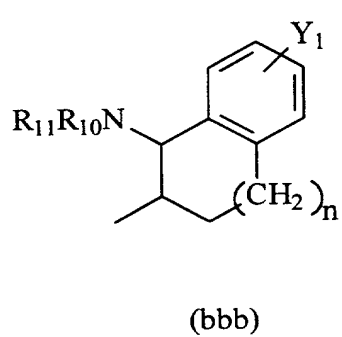
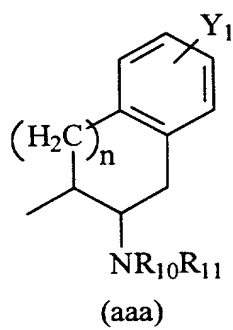
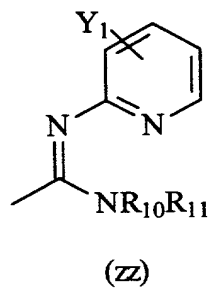
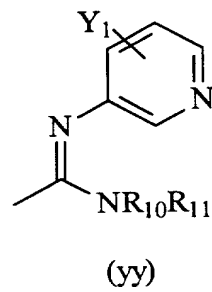
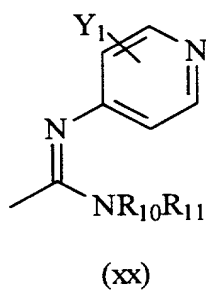
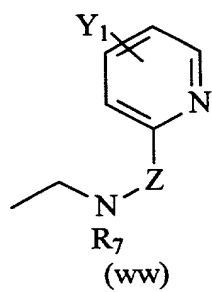
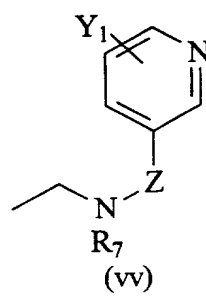
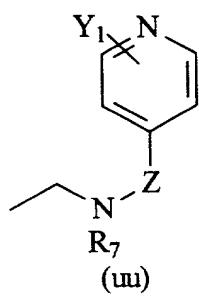
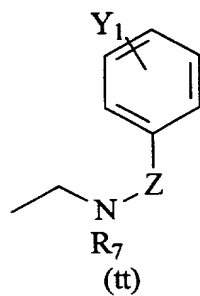


(ii)



(ij)





X₁ is hydrogen, C₁₋₈ alkyl, C₃₋₈alkenyl, C₃₋₈alkynyl;

X₂ is hydrogen, C₁₋₈alkyl, C₃₋₈alkenyl, C₃₋₈alkynyl;

or X₁ and X₂ together form =O, =S, =NH;

R₇ is H, C₁₋₈alkyl, CH₂aryl substituted by one or more substituents Y₁, NR₁₀R₁₁,

5 NHCOR₁₂, NHCO₂R₁₃, CONR₁₄R₁₅, CH₂(CH₂)_nY₂, C(=NH)NR₁₆R₁₇.

R₈ is H, C₁₋₈alkyl, CH₂aryl substituted by one or more substituents Y₁, CONR₁₃R₁₄,

CH₂(CH₂)_nY₂.

R₉ is H, C₁₋₈ alkyl, CH₂ aryl substituted by one or more substituents Y₁, CH₂(CH₂)_nY₂;

R₁₀ is H, C₁₋₈ alkyl, CH₂ aryl substituted by one or more substituents Y₁, CH₂(CH₂)_nY₂.

10 R₁₁ is H, C₁₋₈ alkyl, CH₂ aryl substituted by one or more substituents Y₁, CH₂(CH₂)_nY₂.

R₁₂ is H, C₁₋₈ alkyl, CH₂ aryl substituted by one or more substituents Y₁, CH₂(CH₂)_nY₂.

R₁₃ is H, C₁₋₈ alkyl, CH₂ aryl substituted by one or more substituents Y₁, CH₂(CH₂)_nY₂.

R₁₄ is H, C₁₋₈ alkyl, CH₂ aryl substituted by one or more substituents Y₁, CH₂(CH₂)_nY₂.

R₁₅ is H, C₁₋₈ alkyl, CH₂ aryl substituted by one or more substituents Y₁, CH₂(CH₂)_nY₂.

R₁₆ is H, C₁₋₈ alkyl, CH₂ aryl substituted by one or more substituents Y₁, CH₂(CH₂)_nY₂.

and

R₁₇ is H, C₁₋₈ alkyl, CH₂ aryl substituted by one or more substituents Y₁, CH₂(CH₂)_nY₂

2. The method of claim 1, wherein said kappa opioid receptor antagonist is a
compound of formula (I), wherein R₁, R₄, R₅, Y₁, Y₂, Z, n, X₁, X₂, and R₇-R₁₇ are as indicated
above;

Y₃ is H;

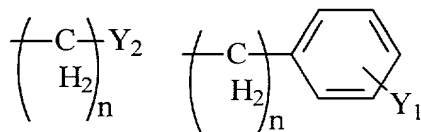
R₂ and R₃ are each, independently, H, C₁₋₈ alkyl, C₃₋₈ alkenyl, C₃₋₈ alkynyl, CH₂aryl
substituted by one or more substituents Y₁; and

R₆ is a group having a formula selected from the group consisting of structures (a)-
(cc).

and pharmaceutically acceptable salts thereof.

3. The method of claim 1, wherein said kappa opioid receptor antagonist is a
compound of formula (I) wherein Y₁, Y₂, R₄, R₅, Z, n, X₁, X₂ and R₈-R₁₅ are as indicated
above;

30 R₁ is C₁₋₈ alkyl,



Y_3 is H;

R_2 and R_3 are each, independently, H or C_{1-8} alkyl, wherein R_2 and R_3 cannot both be H at the same time;

R_6 is a formula selected from the structures (a)-(r); and

R_7 is H, C_{1-8} alkyl, CH_2 aryl substituted by one or more substituents Y_1 , $\text{NR}_{10}\text{R}_{11}$, NHCOR_{12} , $\text{NHCO}_2\text{R}_{13}$, $\text{CONR}_{14}\text{R}_{15}$, or $\text{CH}_2(\text{CH}_2)_n\text{Y}_2$.

4. The method of claim 1, wherein said kappa opioid receptor antagonist is a compound of formula (I) wherein Y_1 , Z, n, X_1 , X_2 and R_8 - R_{15} are as noted above;

R_1 is C_{1-8} alkyl;

Y_2 is H, CF_3 , CO_2R_9 , C_{1-6} alkyl, $\text{NR}_{10}\text{R}_{11}$, NHCOR_{12} , $\text{NHCO}_2\text{R}_{12}$, $\text{CONR}_{13}\text{R}_{14}$, CH_2OH , CH_2OR_8 , COCH_2R_9 ;

Y_3 is H;

R_2 and R_3 are each, independently, H or methyl, wherein R_2 and R_3 cannot both be H at the same time;

R_4 is H, C_{1-8} alkyl, $\text{CO}_2\text{C}_{1-8}$ alkyl, aryl substituted by one or more substituents Y_1 and the stereocenter adjacent to R_4 is in an (S) configuration;

R_5 is H, C_{1-8} alkyl, $\text{CH}_2\text{CO}_2\text{C}_{1-8}$ alkyl;

R_6 is a group having a formula selected from the group consisting of structures (a)-(c) and (h)-(o); and

R_7 is H, C_{1-8} alkyl, CH_2 aryl substituted by one or more substituents Y_1 , $\text{NR}_{10}\text{R}_{11}$, NHCOR_{12} , $\text{NHCO}_2\text{R}_{13}$, $\text{CONR}_{14}\text{R}_{15}$, or $\text{CH}_2(\text{CH}_2)_n\text{Y}_2$.

5. The method of claim 1, wherein said kappa opioid receptor antagonist is a compound of formula (I), wherein Y_1 , Z, n, X_1 , X_2 and R_8 - R_{14} are as indicated above;

R₁ is methyl,

Y₂ is H, CF₃, CO₂R₉, C₁₋₆ alkyl, NR₁₀R₁₁, NHCOR₁₂, NHCO₂R₁₂, CONR₁₃R₁₄,
CH₂OH, CH₂OR₈, COCH₂R₉;

Y₃ is H;

5 R₂ and R₃ are each H or methyl, such that when R₂ is H, R₃ is methyl and vice versa;
R₄ is C₁₋₈ alkyl, CO₂C₁₋₈ alkyl, and the stereocenter adjacent to R₄ has a configuration
of (S);

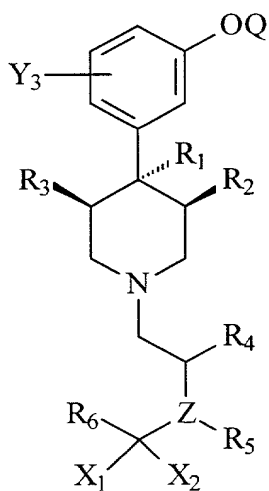
R₅ is H;

10 R₆ is a group having a formula selected from the group consisting of structures (a) and
(b); and

R₇ is H, C₁₋₈ alkyl, CH₂aryl substituted by one or more substituents Y₁ or
CH₂(CH₂)_nY₂.

6. The method of claim 1, wherein said kappa opioid receptor antagonist is a
compound selected from formulae **14-21** of Fig. 1.

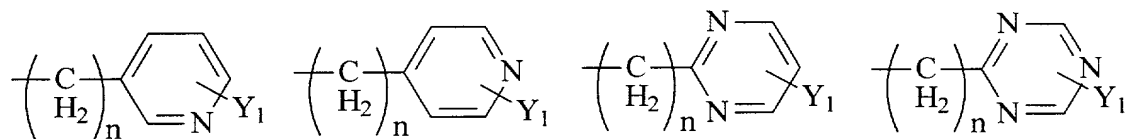
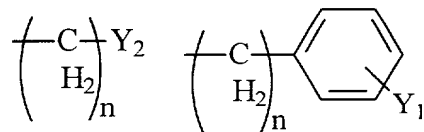
7. A kappa opioid receptor antagonist compound represented by the formula (I):



(I)

wherein Q is H or COC₁₋₈ alkyl;

R₁ is C₁₋₈ alkyl, or one of the following structures:



Y₁ is H, OH, Br, Cl, F, CN, CF₃, NO₂, N₃, OR₈, CO₂R₉, C₁₋₆ alkyl, NR₁₀R₁₁, NHCOR₁₂, NHCO₂R₁₂, CONR₁₃R₁₄, CH₂(CH₂)_nY₂;

Y₂ is H, CF₃, CO₂R₉, C₁₋₆alkyl, NR₁₀R₁₁, NHCOR₁₂, NHCO₂R₁₂, CONR₁₃R₁₄, CH₂OH, CH₂OR₈, COCH₂R₉;

Y₃ is H, OH, Br, Cl, F, CN, CF₃, NO₂, N₃, OR₈, CO₂R₉, C₁₋₆ alkyl, NR₁₀R₁₁, NHCOR₁₂, NHCO₂R₁₂, CONR₁₃R₁₄, CH₂(CH₂)_nY₂;

R₂ is H, C₁₋₈ alkyl, C₃₋₈ alkenyl, C₃₋₈ alkynyl or CH₂aryl substituted by one or more groups Y₁;

R₃ is H, C₁₋₈ alkyl, C₃₋₈ alkenyl, C₃₋₈ alkynyl or CH₂aryl substituted by one or more groups Y₁;

wherein R₂ and R₃ may be bonded together to form a C₂₋₈ alkyl group;

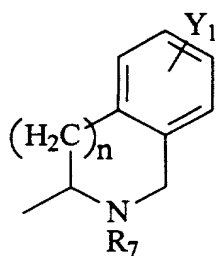
R₄ is hydrogen, C₁₋₈ alkyl, CO₂C₁₋₈ alkylaryl substituted by one or more groups Y₁, CH₂aryl substituted by one or more groups Y₁ or CO₂C₁₋₈ alkyl;

Z is N, O or S; when Z is O or S there is no R₅

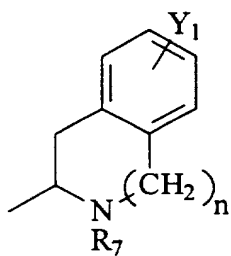
R₅ is H, C₁₋₈ alkyl, C₃₋₈ alkenyl, C₃₋₈ alkynyl, CH₂CO₂C₁₋₈ alkyl, CO₂C₁₋₈ alkyl or CH₂aryl substituted by one or more groups Y₁;

n is 0, 1, 2 or 3;

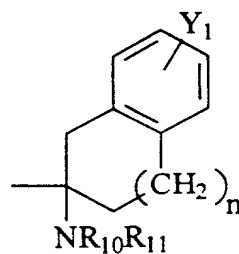
R₆ is a group selected from the group consisting of structures (a)-(bbb):



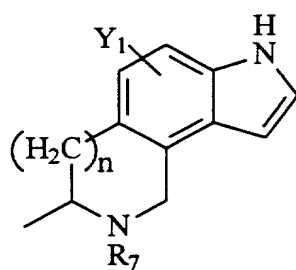
(a)



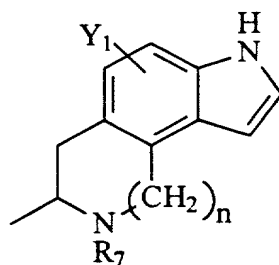
(b)



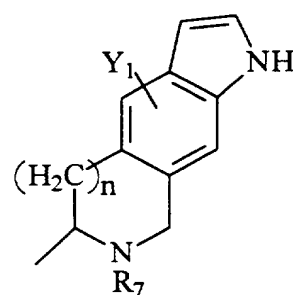
(c)



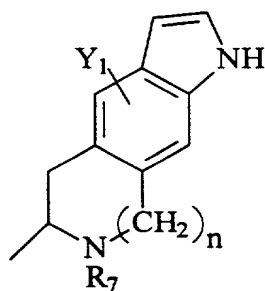
(d)



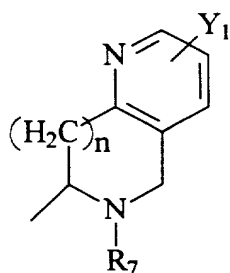
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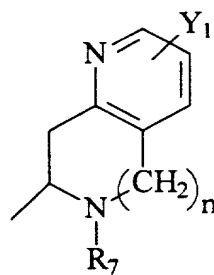
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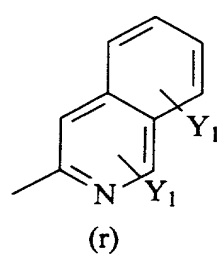
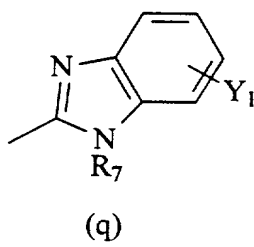
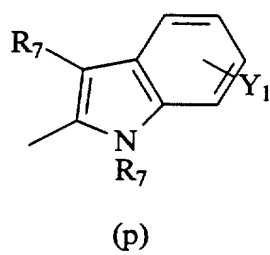
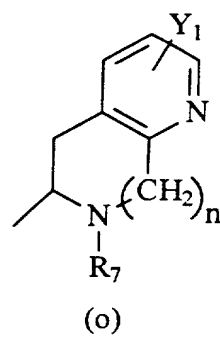
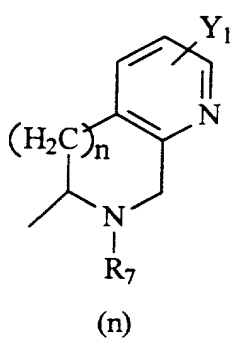
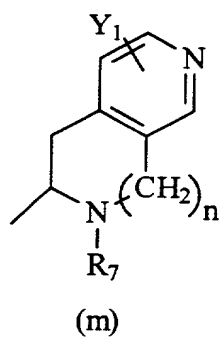
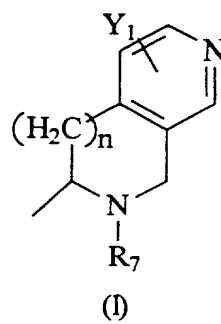
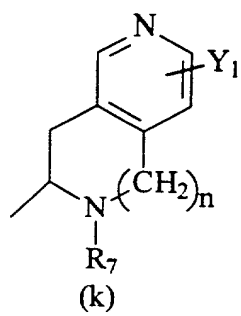
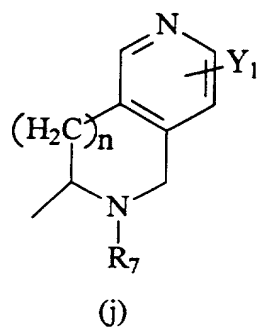
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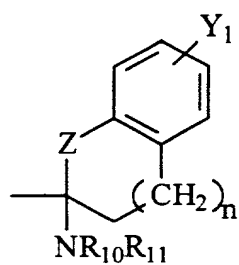


(h)

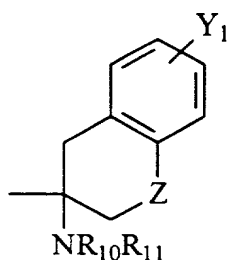


(i)

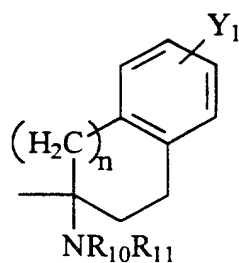




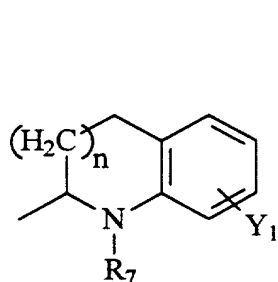
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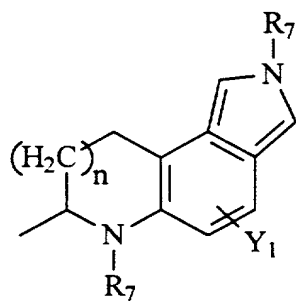
(t)



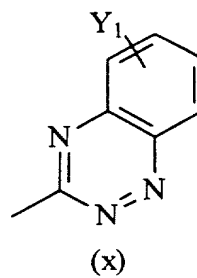
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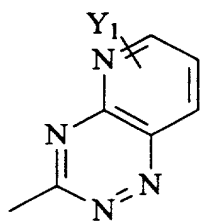
(v)



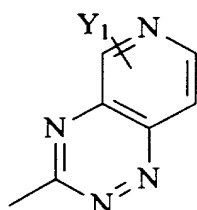
(w)



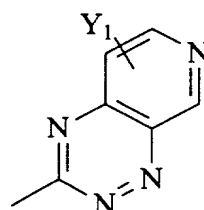
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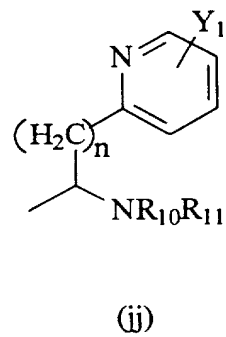
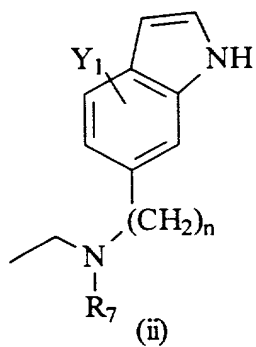
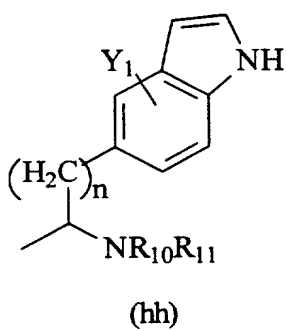
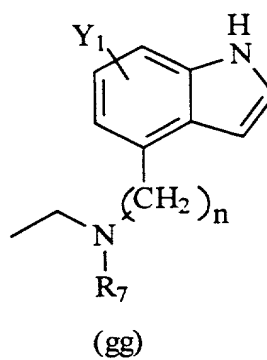
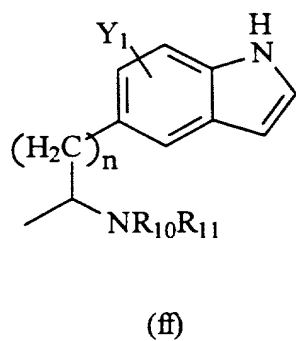
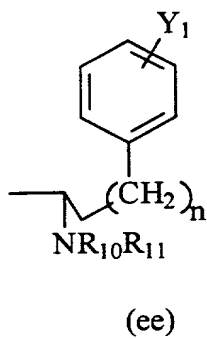
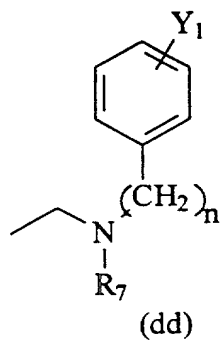
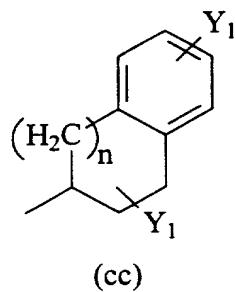
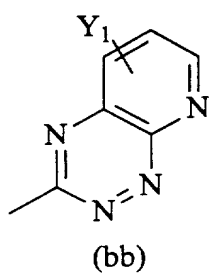
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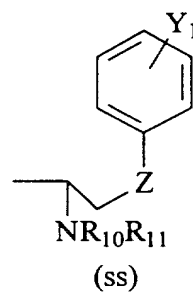
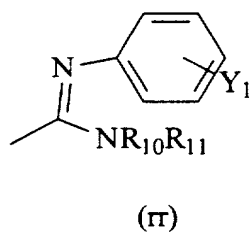
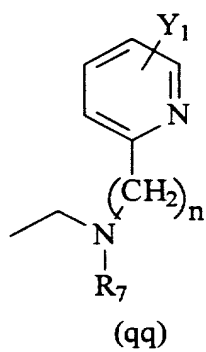
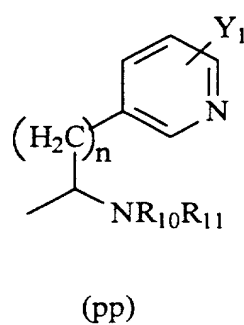
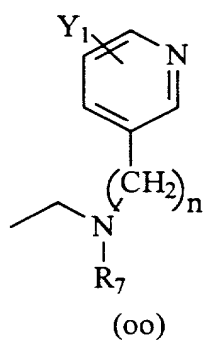
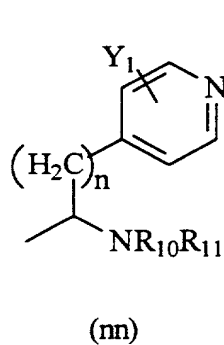
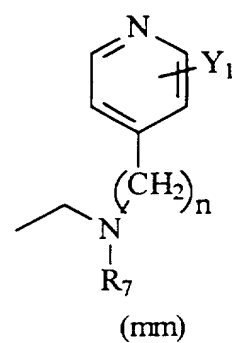
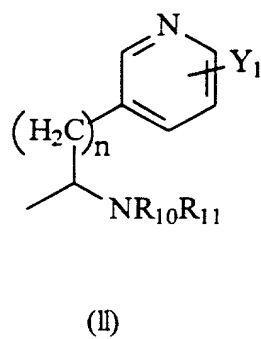
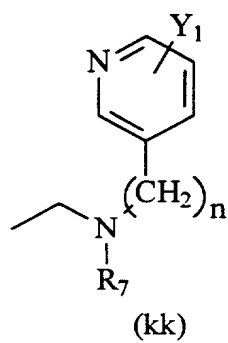


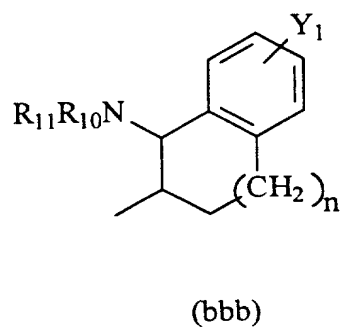
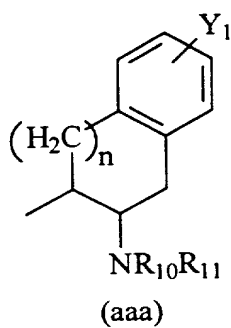
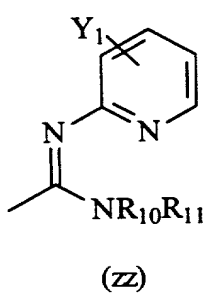
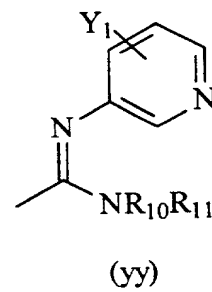
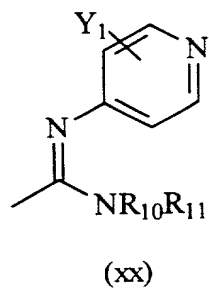
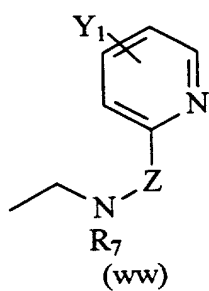
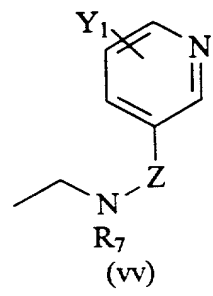
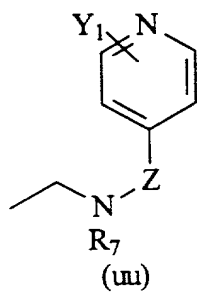
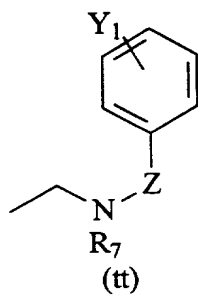
(z)



(aa)







X₁ is hydrogen, C₁₋₈ alkyl, C₃₋₈alkenyl, C₃₋₈alkynyl;

X₂ is hydrogen, C₁₋₈alkyl, C₃₋₈alkenyl, C₃₋₈alkynyl;

or X₁ and X₂ together form =O, =S, =NH;

R₇ is H, C₁₋₈alkyl, CH₂aryl substituted by one or more substituents Y₁, NR₁₀R₁₁,

5 NHCOR₁₂, NHCO₂R₁₃, CONR₁₄R₁₅, CH₂(CH₂)_nY₂, C(=NH)NR₁₆R₁₇.

R₈ is H, C₁₋₈alkyl, CH₂aryl substituted by one or more substituents Y₁, CONR₁₃R₁₄,

CH₂(CH₂)_nY₂.

R₉ is H, C₁₋₈ alkyl, CH₂ aryl substituted by one or more substituents Y₁, CH₂(CH₂)_nY₂;

R₁₀ is H, C₁₋₈ alkyl, CH₂ aryl substituted by one or more substituents Y₁, CH₂(CH₂)_nY₂.

10 R₁₁ is H, C₁₋₈ alkyl, CH₂ aryl substituted by one or more substituents Y₁, CH₂(CH₂)_nY₂.

R₁₂ is H, C₁₋₈ alkyl, CH₂ aryl substituted by one or more substituents Y₁, CH₂(CH₂)_nY₂.

R₁₃ is H, C₁₋₈ alkyl, CH₂ aryl substituted by one or more substituents Y₁, CH₂(CH₂)_nY₂.

R₁₄ is H, C₁₋₈ alkyl, CH₂ aryl substituted by one or more substituents Y₁, CH₂(CH₂)_nY₂.

R₁₅ is H, C₁₋₈ alkyl, CH₂ aryl substituted by one or more substituents Y₁, CH₂(CH₂)_nY₂.

R₁₆ is H, C₁₋₈ alkyl, CH₂ aryl substituted by one or more substituents Y₁, CH₂(CH₂)_nY₂.

and

R₁₇ is H, C₁₋₈ alkyl, CH₂ aryl substituted by one or more substituents Y₁, CH₂(CH₂)_nY₂
and pharmaceutically acceptable salts thereof.

8. The kappa opioid receptor antagonist compound of claim 7, wherein R₁, R₄, R₅, Y₁,
20 Y₂, Z, n, X₁, X₂, and R₇-R₁₇ are as indicated above;

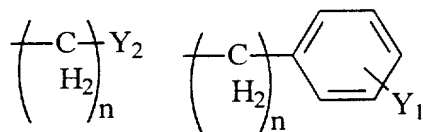
Y₃ is H;

R₂ and R₃ are each, independently, H, C₁₋₈ alkyl, C₃₋₈ alkenyl, C₃₋₈ alkynyl, CH₂aryl
substituted by one or more substituents Y₁; and

R₆ is a group having a formula selected from the group consisting of structures (a)-
25 (cc).

9. The kappa opioid receptor antagonist compound of claim 7, wherein Y₁, Y₂, R₄, R₅,
Z, n, X₁, X₂ and R₈-R₁₅ are as indicated above;

R₁ is C₁₋₈ alkyl,



Y₃ is H;

R₂ and R₃ are each, independently, H or C₁₋₈ alkyl, wherein R₂ and R₃ cannot both be H at the same time;

R₆ is a formula selected from the structures (a)-(r) shown above; and

5 R₇ is H, C₁₋₈ alkyl, CH₂aryl substituted by one or more substituents Y₁, NR₁₀R₁₁, NHCOR₁₂, NHCO₂R₁₃, CONR₁₄R₁₅, or CH₂(CH₂)_nY₂.

10. The kappa opioid receptor antagonist compound of claim 7, wherein Y₁, Z, n, X₁, X₂ and R₈-R₁₅ are as noted above;

R₁ is C₁₋₈ alkyl;

10 Y₂ is H, CF₃, CO₂R₉, C₁₋₆ alkyl, NR₁₀R₁₁, NHCOR₁₂, NHCO₂R₁₂, CONR₁₃R₁₄, CH₂OH, CH₂OR₈, COCH₂R₉;

Y₃ is H;

R₂ and R₃ are each, independently, H or methyl, wherein R₂ and R₃ cannot both be H at the same time;

15 R₄ is H, C₁₋₈ alkyl, CO₂C₁₋₈alkyl, aryl substituted by one or more substituents Y₁ and the stereocenter adjacent to R₄ is in an (S) configuration;

R₅ is H, C₁₋₈ alkyl, CH₂CO₂C₁₋₈ alkyl;

R₆ is a group having a formula selected from the group consisting of structures (a)-(c) and (h)-(o); and

20 R₇ is H, C₁₋₈alkyl, CH₂aryl substituted by one or more substituents Y₁, NR₁₀R₁₁, NHCOR₁₂, NHCO₂R₁₃, CONR₁₄R₁₅, or CH₂(CH₂)_nY₂.

11. The kappa opioid receptor antagonist compound of claim 7, wherein Y₁, Z, n, X₁, X₂ and R₈-R₁₄ are as indicated above;

R₁ is methyl,

25 Y₂ is H, CF₃, CO₂R₉, C₁₋₆ alkyl, NR₁₀R₁₁, NHCOR₁₂, NHCO₂R₁₂, CONR₁₃R₁₄, CH₂OH, CH₂OR₈, COCH₂R₉;

Y₃ is H;

R₂ and R₃ are each H or methyl, such that when R₂ is H, R₃ is methyl and vice versa;

R_4 is C_{1-8} alkyl, CO_2C_{1-8} alkyl, and the stereocenter adjacent to R_4 has a configuration of (S);

R_5 is H;

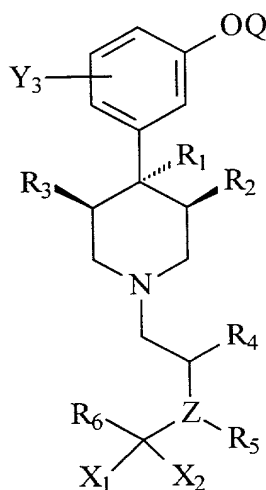
R_6 is a group having a formula selected from the group consisting of structures (a) and (b); and

R_7 is H, C_{1-8} alkyl, CH_2 aryl substituted by one or more substituents Y_1 or $CH_2(CH_2)_nY_2$.

12. The kappa opioid receptor antagonist of claim 7, wherein said compound is a compound selected from formulae **14-21** of Fig. 1.

13. A pharmaceutical composition comprising:

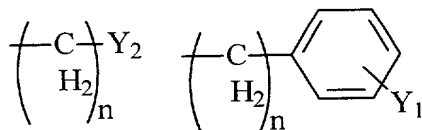
an effective amount of a kappa opioid receptor antagonist and a physiologically acceptable carrier, wherein the kappa opioid receptor antagonist is a compound of formula (I):

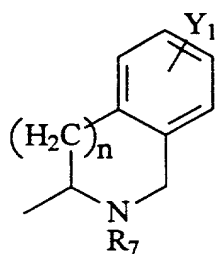


(I)

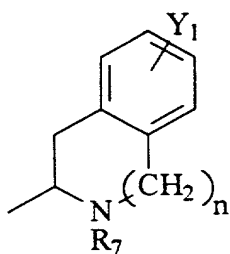
wherein Q is H or $CO C_{1-8}$ alkyl;

R_1 is C_{1-8} alkyl, or one of the following structures:

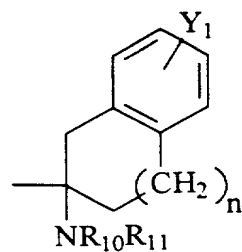




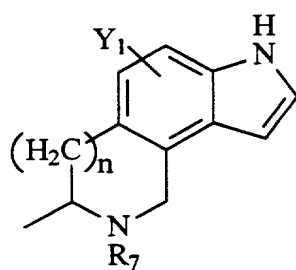
(a)



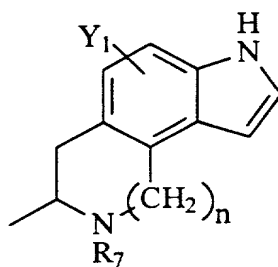
(b)



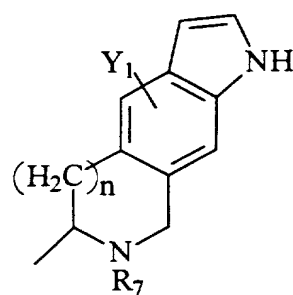
(c)



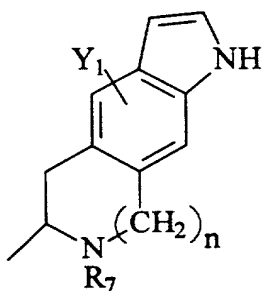
(d)



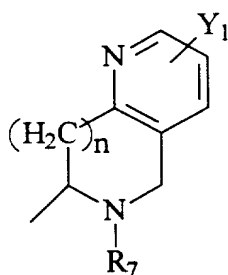
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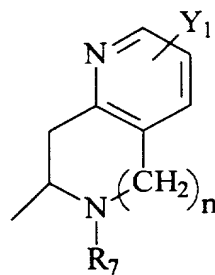
(f)



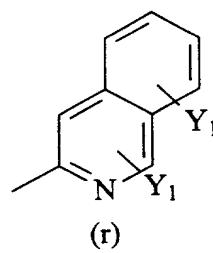
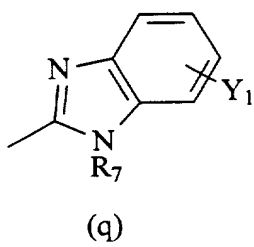
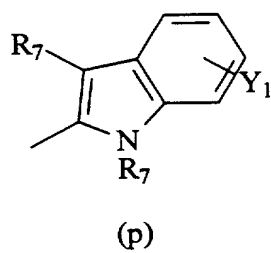
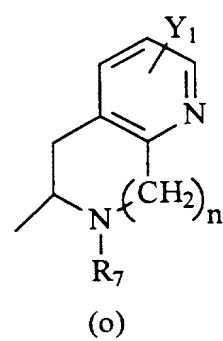
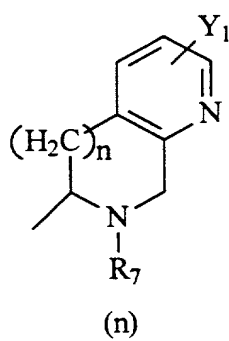
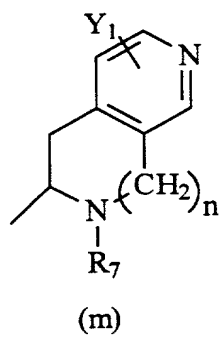
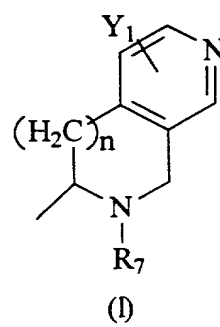
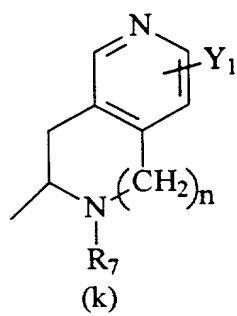
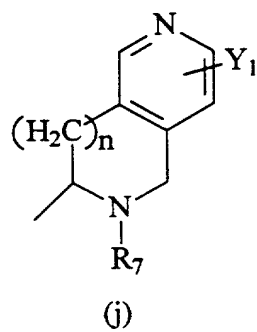
(g)

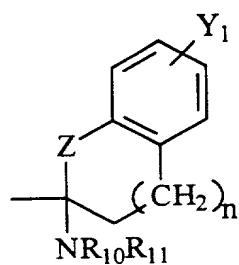


(h)

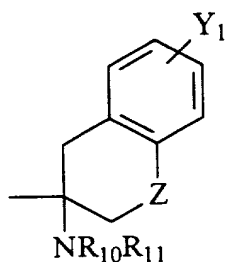


(i)

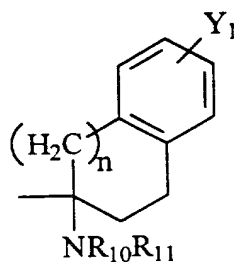




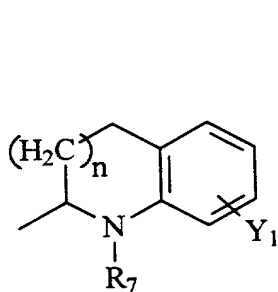
(s)



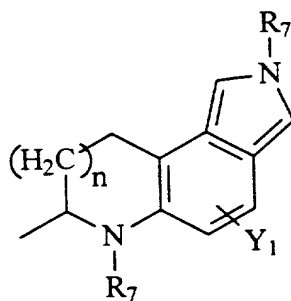
(t)



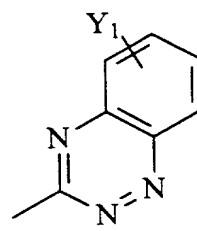
(u)



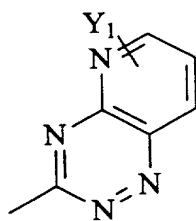
(v)



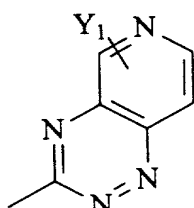
(w)



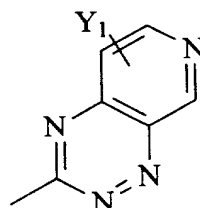
(x)



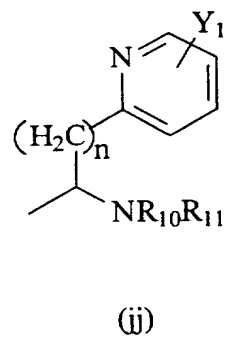
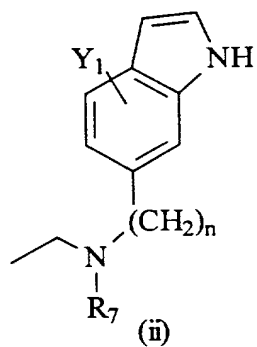
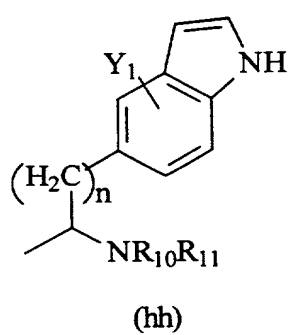
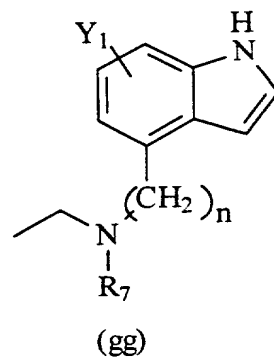
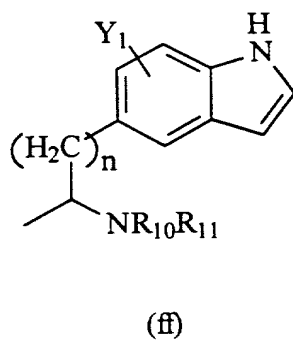
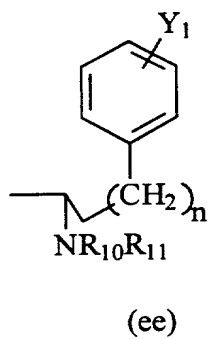
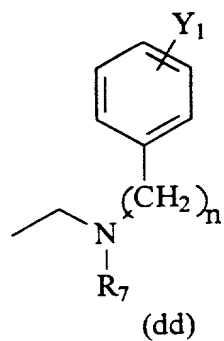
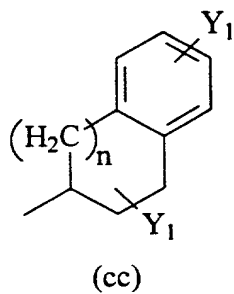
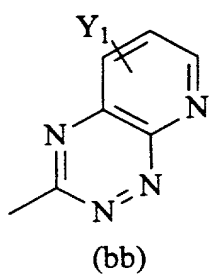
(y)

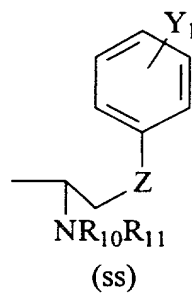
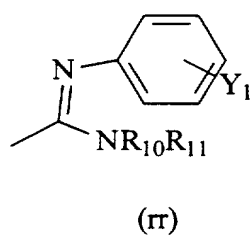
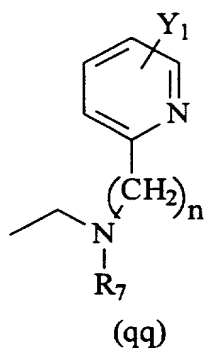
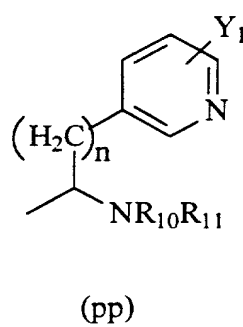
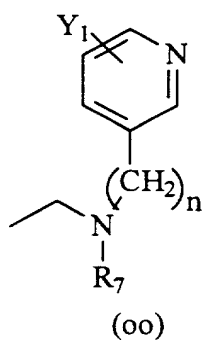
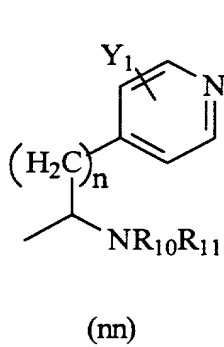
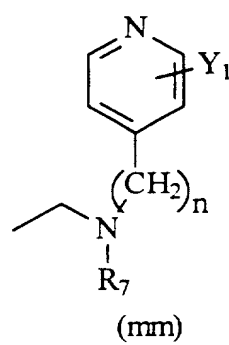
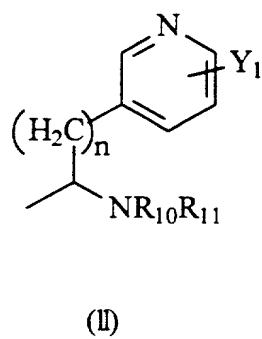
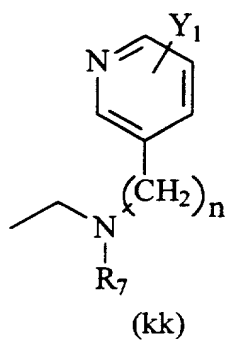


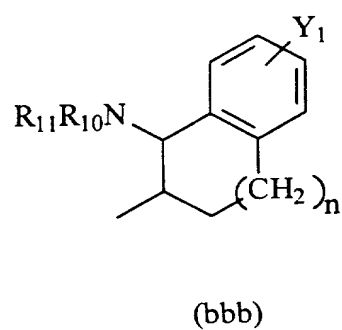
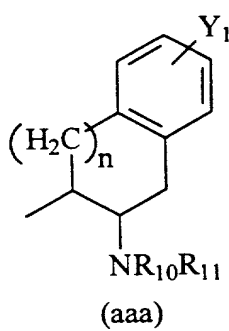
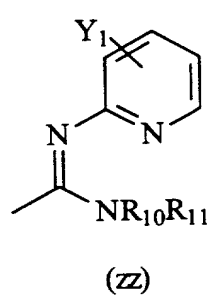
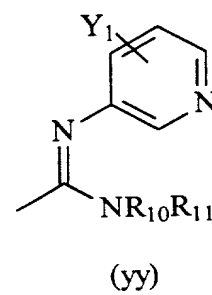
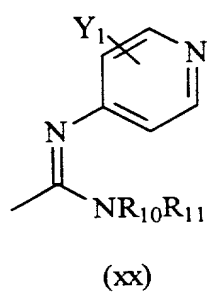
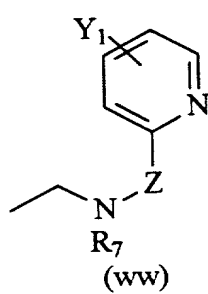
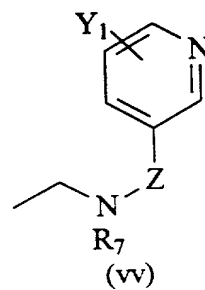
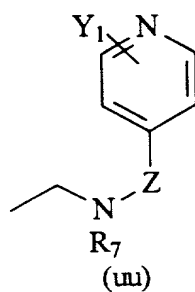
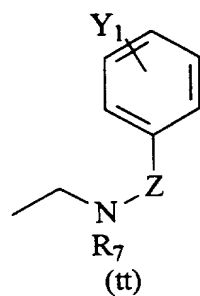
(z)



(aa)







X₁ is hydrogen, C₁₋₈ alkyl, C₃₋₈alkenyl, C₃₋₈alkynyl;

X₂ is hydrogen, C₁₋₈alkyl, C₃₋₈alkenyl, C₃₋₈alkynyl;

or X₁ and X₂ together form =O, =S, =NH;

R₇ is H, C₁₋₈alkyl, CH₂aryl substituted by one or more substituents Y₁, NR₁₀R₁₁,

5 NHCOR₁₂, NHCO₂R₁₃, CONR₁₄R₁₅, CH₂(CH₂)_nY₂, C(=NH)NR₁₆R₁₇.

R₈ is H, C₁₋₈alkyl, CH₂aryl substituted by one or more substituents Y₁, CONR₁₃R₁₄,

CH₂(CH₂)_nY₂.

R₉ is H, C₁₋₈ alkyl, CH₂ aryl substituted by one or more substituents Y₁, CH₂(CH₂)_nY₂;

R₁₀ is H, C₁₋₈ alkyl, CH₂ aryl substituted by one or more substituents Y₁, CH₂(CH₂)_nY₂.

10 R₁₁ is H, C₁₋₈ alkyl, CH₂ aryl substituted by one or more substituents Y₁, CH₂(CH₂)_nY₂.

R₁₂ is H, C₁₋₈ alkyl, CH₂ aryl substituted by one or more substituents Y₁, CH₂(CH₂)_nY₂.

R₁₃ is H, C₁₋₈ alkyl, CH₂ aryl substituted by one or more substituents Y₁, CH₂(CH₂)_nY₂.

R₁₄ is H, C₁₋₈ alkyl, CH₂ aryl substituted by one or more substituents Y₁, CH₂(CH₂)_nY₂.

R₁₅ is H, C₁₋₈ alkyl, CH₂ aryl substituted by one or more substituents Y₁, CH₂(CH₂)_nY₂.

15 R₁₆ is H, C₁₋₈ alkyl, CH₂ aryl substituted by one or more substituents Y₁, CH₂(CH₂)_nY₂.

and

R₁₇ is H, C₁₋₈ alkyl, CH₂ aryl substituted by one or more substituents Y₁, CH₂(CH₂)_nY₂

or a pharmaceutically acceptable salt thereof.

14. The pharmaceutical composition of claim 13, wherein said kappa opioid receptor
20 antagonist is a compound of formula (I), wherein R₁, R₄, R₅, Y₁, Y₂, Z, n, X₁, X₂, and R₇-R₁₇
are as indicated above;

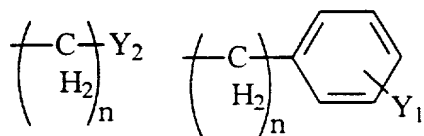
Y₃ is H;

R₂ and R₃ are each, independently, H, C₁₋₈ alkyl, C₃₋₈ alkenyl, C₃₋₈ alkynyl, CH₂aryl
substituted by one or more substituents Y₁; and

25 R₆ is a group having a formula selected from the group consisting of structures (a)-
(cc).

15. The pharmaceutical composition of claim 13, wherein said kappa opioid receptor
antagonist is a compound of formula (I), wherein Y₁, Y₂, R₄, R₅, Z, n, X₁, X₂ and R₈-R₁₅ are as
indicated above;

30 R₁ is C₁₋₈ alkyl,



Y₃ is H;

R₂ and R₃ are each, independently, H or C₁₋₈ alkyl, wherein R₂ and R₃ cannot both be H at the same time;

R₆ is a formula selected from the structures (a)-(r) shown above; and

R₇ is H, C₁₋₈ alkyl, CH₂aryl substituted by one or more substituents Y₁, NR₁₀R₁₁, NHCOR₁₂, NHCO₂R₁₃, CONR₁₄R₁₅, or CH₂(CH₂)_nY₂.

16. The pharmaceutical composition of claim 13, wherein said kappa opioid receptor antagonist is a compound of formula (I), wherein Y₁, Z, n, X₁, X₂ and R₈-R₁₅ are as noted above;

R₁ is C₁₋₈ alkyl;

Y₂ is H, CF₃, CO₂R₉, C₁₋₆ alkyl, NR₁₀R₁₁, NHCOR₁₂, NHCO₂R₁₂, CONR₁₃R₁₄, CH₂OH, CH₂OR₈, COCH₂R₉;

Y₃ is H;

R₂ and R₃ are each, independently, H or methyl, wherein R₂ and R₃ cannot both be H at the same time;

R₄ is H, C₁₋₈ alkyl, CO₂C₁₋₈alkyl, aryl substituted by one or more substituents Y₁ and the stereocenter adjacent to R₄ is in an (S) configuration;

R₅ is H, C₁₋₈ alkyl, CH₂CO₂C₁₋₈ alkyl;

R₆ is a group having a formula selected from the group consisting of structures (a)-(c) and (h)-(o); and

R₇ is H, C₁₋₈alkyl, CH₂aryl substituted by one or more substituents Y₁, NR₁₀R₁₁, NHCOR₁₂, NHCO₂R₁₃, CONR₁₄R₁₅, or CH₂(CH₂)_nY₂.

17. The pharmaceutical composition of claim 13, wherein said kappa opioid receptor antagonist is a compound of formula (I), wherein Y_1 , Z, n, X_1 , X_2 and R_8 - R_{14} are as indicated above;

R_1 is methyl,

Y_2 is H, CF_3 , CO_2R_9 , C_{1-6} alkyl, $NR_{10}R_{11}$, $NHCO_2R_{12}$, $CONR_{13}R_{14}$, CH_2OH , CH_2OR_8 , $COCH_2R_9$;

Y_3 is H;

R_2 and R_3 are each H or methyl, such that when R_2 is H, R_3 is methyl and vice versa;

R_4 is C_{1-8} alkyl, CO_2C_{1-8} alkyl, and the stereocenter adjacent to R_4 has a configuration of (S);

R_5 is H;

R_6 is a group having a formula selected from the group consisting of structures (a) and (b); and

R_7 is H, C_{1-8} alkyl, CH_2 aryl substituted by one or more substituents Y_1 or $CH_2(CH_2)_nY_2$.

18. The pharmaceutical composition of claim 13, wherein said kappa opioid receptor antagonist is a compound selected from formulae 14-21 of Fig. 1.

19. The pharmaceutical composition of claim 13, wherein said composition is an injectable composition.

20. The pharmaceutical composition of claim 13, wherein said composition is an orally administrable composition.

21. The pharmaceutical composition of claim 20, wherein said orally administrable composition is in a form selected from the group consisting of tablets, capsules, troches, powders, solutions, dispersions, emulsions and suspensions.